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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,886	05/15/2001	Barry Coller	A31386-A	1518

21003 7590 10/16/2003

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/855,886	Applicant(s) COLLER ET AL	
	Examin r Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claim 4 has been canceled.

Claims 15 to 17 have been added. **NOTE**: in the amendment filed 7/11/03 claims 12-14 were added, however, claims 12-14 were canceled in the preliminary amendment filed with the application. Therefore under Rule 1.126 added claims 12-14 were renumbered claims 15-17.

Claim 1 has been amended.

2. Claims 103, 5-11 and 15-17 are pending and under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

5. The rejection of claims 1-3, 5-11 under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (Blood, Vol. 89 (1997), pp 4078-4084, Information Disclosure Statement #8) and Coller et al (Haemostasis (1996) 26, pp 285-293, IDS #8) further in view of Friedlander et al (Proc Natl. Acad. Sci. U.S.A. 93 (1996), pp 9764-9769, IDS #8), and Brooks et al (US 5, 753, 230, Filed Mar. 18, 1994, IDS #8) is withdrawn in view of the new ground of rejection.

Response to Arguments

6. The rejection of claims 1-2 and 5-11 under 35 U.S.C. 112, first paragraph, is maintained.

The response filed 7/11/03 has been carefully considured but is deemed not to be persuasive. The amended claims are still broadly drawn to a method for inhibiting angiogenesis in a mammal comprising administering a monoclonal antibody or fragment which acts as an antagonist of GPIIb/IIIa and alphaVbeta3. The claims are broadly drawn to administering any antibody that is an antagonist of integrins GPIIb/IIIa and alphavbeta3.

The response filed 7/11/03 has been carefully considured but is deemed not to be persuasive. The response states that the methods for identifying molecules that bind to and antgonize the recited integrins were standard techniques known in the art and there is no reason to conclude that 7E3 is the only possible antibody with the claimed properties and the fact that AP3 and LM609 both lack the properties is not relevant (see pages 5-6 of response). In response to this argument, while it may be routine to screen large numbers of clones for a particular affinity or properties, as stated in the previous Office Action, the specification has not demonstrated the reproducible production of antibodies which have the properties identical to 7E3 and recited in claim 1. In addition the response does not address the art of Reverter et al (J. Clin Invest. (1996) 98, pp 863-874, Invention Disclosure Statement # 8) which state that "the combined inhibitory effect of 10E5 and LM609 did not equal that produced by 7E3 alone"(page 872, left column first full paragraph), further in indicating that 7E3 has the unique feature of inhibiting both integrins GPIIb/IIIa and alphaV beta3 that one does not observe with

either 10E5, LM609, or AP3. Thus, it appears that the 7E3 antibody has unique properties of binding to both integrins GPIIb/IIIa and alphaV beta3 and acting as antagonist is a property apparently unique to only this 7E3 antibody. Therefore, reasonable doubt exists as to whether the isolation of the monoclonal antibody may have been fortuitous and not reproducible without undue experimentation. Filing of evidence of the reproducibility of the claimed monoclonal antibodies without undue experimentation coupled with evidence of the public availability of the starting materials necessary to produce the claimed antibodies is accordingly required.

Alternatively, amending the independent claims to recite "wherein the antibody or antigen binding fragment thereof is 7E3" may be sufficient to obviate this rejection.

The following is a NEW GROUND of rejection

7. Claims 1-3, 5-11, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Max et al (Int. J. Cancer 71:320-324, 5/1997) further in view of Taylor et al (Blood, Vol. 89 (1997), pp 4078-4084, Information Disclosure Statement #8) and Mohle et al (PNAS 94:663-668, 1/97) and Charo et al (The Journal of Biological Chemistry 262:9935-9938, 1987) as evidenced by Coller et al (Haemostasis (1996) 26, pp 285-293, IDS #8).

The claims are drawn to a method for inhibiting angiogenesis in a mammal comprising administering a monoclonal antibody or fragment which acts as an antagonist of the integrins GPIIb/IIIa and alphaV beta3 wherein the antibody is 7E3 or a

mouse/human chimeric thereof and has the characteristics recited in claim 1 and the antibody is administered intravenously, in an amount of about 0.25 mg/kg followed by infusion of 0.125 mk/kg/min of antibody, wherein the mammal is a primate or dog or cat or human, and method treats inflammatory disease from group consisting of rheumatoid arthritis, macular degeneration, psoriasis, diabetic retinopathy.

Max et al teach expression of alphaVbeta3 on tumor cells and cells involved in angiogenesis and angiogenesis contributes to diabetic retinopathy and an antibody to alphaVbeta3 detected the integrin in the cells and that tumors can be treated with alphaVbeta3 antagonists. Max et al does not teach administration of 7E3 intravenous at the claimed amount to treat an inflammatory disease such as diabetic retinopathy. These deficiencies are made up for by the teachings of Taylor et al, Charo et la and Mohle et al.

Taylor et al teach the use of 7E3 f(ab')2 as well as the chimeric mouse/human c7E3 antibodies for the protection against microangiopathic hemolytic anemia and microvasular thrombotic renal failure in Baboons. Taylor et al also teach administering the antibody intravenously, in a 0.25 mg/kg amount, or in the amount of about 0.25 mg/kg body weight followed by infusion of 0.25 to 0.35 mg/kg over 6 hours (page 4079) to a baboon.

Charo et al teach administration of 7E3 inhibits platelet aggregation by binding to GPIIb/IIIa.

Mohle et al teach VEGF is produced from activated platelets and VEGF is delivered to the site of injury by activated platelets and this may initiate angiogenesis (see abstract)

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the 7E3 antibody, that are antagonist of integrins GPIIb/IIIa and alphaV beta3 in methods of intravenous administration at the amounts taught explicitly by Taylor et al for inhibiting angiogenesis/inflammatory diseases in a human in view of Max, Mohle, and Charo.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the 7E3 antibody or fragments or chimeras that are antagonist of integrins GPIIb/IIIa and alphaV beta3 in methods of intravenous administration at the amounts taught explicitly by Taylor et al for inhibiting angiogenesis/inflammatory diseases in a human because Max et al teach that angiogenesis involves the alphaVbeta3 integrin and angiogenesis is involved in cancer and diabetic retinopathy and that antibodies to alphaVbeta3 can be used as antagonists and alphaVbeta3 is a target for cancer and other diseases characterized by angiogenesis (see page 320). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the 7E3 antibody or fragments or chimeras that are antagonist of integrins GPIIb/IIIa and alphaV beta3 in methods of intravenous administration at the amounts taught explicitly by Taylor et al for inhibiting angiogenesis/inflammatory diseases in a human because Mohle et al teach VEGF is delivered to the site of injury by activated platelets and this

may initiate angiogenesis and because Charo et al teach that 7E3, which as evidenced by Coller et al all forms of 7E3 inhibit the function of alphaVbeta3 and GPIIb/IIIa (see page 287), inhibits platelet aggregation. Thus, it would have been obvious to use the 7E3 antibody to inhibit aggregation in a mammal because the art recognized angiogenesis was involved in diabetic retinopathy and cancer and that alphaVbeta3 integrin was involved in angiogenesis and the art recognized that VEGF is an angiogenic factor and is released upon aggregation of platelets and 7E3 inhibited platelet aggregation. Therefore, it would have been obvious to use the 7E3 antibody to inhibit the alphaVbeta3 and GPIIb/IIIa integrins in a method of inhibiting angiogenesis since both integrins are recognized in the art as being involved in angiogenesis.

Although claim 1 recites specific characteristics of the antibody, it would be obvious that the 7E3 antibody have the claimed properties.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 7/11/03 has been carefully considured but is deemed not to be persuasive. The response is directed to the rejection using Taylor, Coller, Frielander, and Brooks, however, that rejection was withdrawn. The response is now only relevant to Taylor and Coller which are still in the rejection above. The response states that Taylor did not provide any motivation to use the &e# to inhibit angiogenesis and Taylors diseases are disorders of blood coagulation or platelet-mediated

coagulation (see page 7 of response). In response to this argument, when combined with the new references Taylor teaches inhibition of platelet aggregation which is known to inhibit VEGF which is involved in angiogenesis. The response also cites publications that 7E3 has improved anti-angiogenic activity (see pages 8-11). In response to this argument, the references do not add anything to the argument and it is not clear what they are intended to demonstrate.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER